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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,451	11/30/2001	Marcel Franz Leopold De Bruyn	JAB-1488	3599

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EXAMINER
COLEMAN, BRENDA LIBBY

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/26/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/980,451	DE BRUYN et al.
Examiner	**Art Unit**
Brenda Coleman	1624

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 11, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7, 9, and 10* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-7, 9, and 10* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-7, 9 and 10 are pending in the application.

Election/Restriction

1. Applicant's election with traverse of Group I in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the compounds of formula (I) share a common utility and a substantial structural feature. This is not found persuasive because while all of the alternatives may have a common property or activity as urged by the applicants, neither element (B)(1) or (B)(2) have been met. The compounds of formula (I) only share one common structural element and that is the presence of a benzene ring which is fused to $-Z^1-Z^2-$ which in itself can be nine different rings which is not a sufficient enough core to indicate a common structure. As for (B)(2) none of the rings or ring systems for A are art recognized equivalents. Note MPEP 2173.05(h) "where a Markush expression is applied only to a portion of a chemical compound, the propriety of the grouping is determined by a consideration of the compound as a whole, and does not depend on there being a community of properties in the members of the Markush expression. Therefore, what should be considered for patentable distinctness is the compound as a whole. Would a whole compound where A is a piperidine be patentably distinct from a whole compound where A is a diazepine ring? If a reference for one would not be a reference for the other, then restriction is considered proper. Community of properties is not enough to keep piperidine, piperazine, diazepine, pyrrole, azepine, etc. in the same Markush claim, where the Markush expression is applied only to a portion of a chemical compound. It is the compound as a

whole piperidine vs diazepine vs piperazine, etc., that must be considered for patentable distinctness.

Thus, separate searches in the literature would be required. However, should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

The requirement is still deemed proper and is therefore made FINAL.

2. Claim 4 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

3. Claims 1, 2, 6, 7, 9 and 10 are rejected as being drawn to an improper Markush group. The recited compounds, while possessing a common utility, differ widely in structure and are not art-recognized equivalents and are thus, independently distinct for the reasons set forth in the restriction above.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-3, 5-7, 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1, 2, 6, 7, 9 and 10 are vague and indefinite in that it is not known what is meant by "a direct bond when the bivalent radical $-Z^1-Z^2-$ is of formula (a-6), (a-7) or (a-8)" in the definition of R^4.

b) Claim 3 is vague and indefinite in that it is not known what is meant by "a compound as claimed in claim 1 R^4 is hydrogen;....". It is believed that the applicants intended a compound as claimed in claim 1 wherein R^4 is hydrogen;....

c) Claim 3 recites the limitation "$-CH_2-CH_2-$ (a-4)" in the definition of $-Z^1-Z^2-$. There is insufficient antecedent basis for this limitation in the claim.

d) Claim 3 recites the limitation "wherein R^{11} is hydroxy or methoxy" in the definition of formula (c-1). There is insufficient antecedent basis for this limitation in the claim.

e) Claim 5 recites the limitation "$-CH_2-CH_2-$ (a-4)" in the definition of $-Z^1-Z^2-$. There is insufficient antecedent basis for this limitation in the claim.

f) Claim 9 is vague and indefinite in that it is not known what is meant by "a process of preparing a compound of formula (I), however there is no formula (I) in the claim or reference to another claim with respect to formula (I).

g) Claim 9 is vague and indefinite in that it is not known what is meant by "an intermediate of formula (II)". There is no formula (II) in the claim.

h) Claim 9 is vague and indefinite in that it is not known what is meant by the reference to the definition of R^4. There is no variable R^4 in the claim.

i) Claim 9 is vague and indefinite in that it is not known what is meant by "compounds of formula (I) are converted into each other following art-known transformation reactions".

j) Claim 7 is vague and indefinite in that it is dependent on two different claims.

k) Claim 10 is vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the conditions related to a hampered or impaired relaxation of the fundus. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given

drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus *iv* or in a time release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are inhibitors *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property which the second drug is capable. It is common for a drug, particularly in dyspepsia, anorexia, etc., to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is (703) 305-1880. The examiner can normally be reached on Mondays from 8:30 AM to 5:00 PM, on Tuesdays from 8:00 AM to 4:30 PM, on Wednesday thru Friday from 9:00 AM to 5:30 PM.

The fax phone number for this Group is (703) 308-4734 for "unofficial" purposes and the actual number for **OFFICIAL** business is **308-4556**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brenda Coleman

Brenda Coleman
Primary Examiner AU 1624
September 25, 2003